Activated Nitriles in Heterocyclic Synthesis: Synthesis of Pyrano[2,3-*d*]pyrimidine and Pyrano[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine Derivatives

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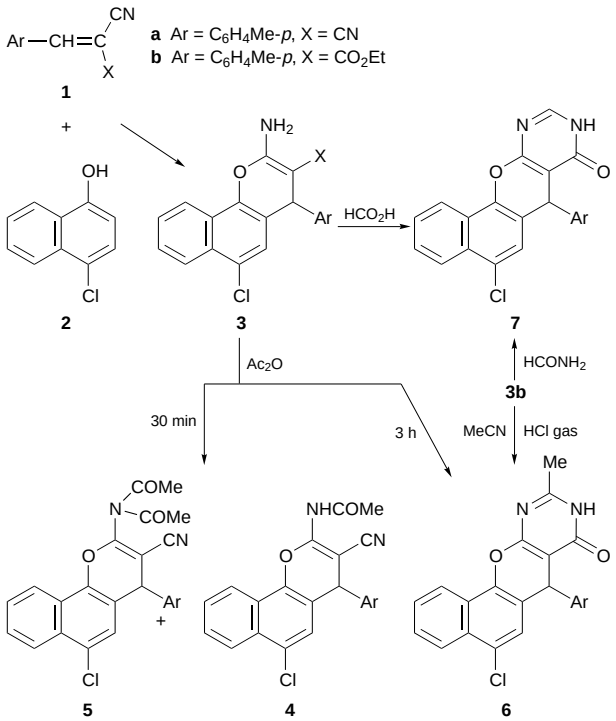
Several new naphtho[2′,1′:5,6]pyrano[2,3-*d*]pyrimidines have been synthesized *via* hydrazinolysis of a 2-ethoxymethylideneaminonaphtho[1,2-*b*]pyran; polysubstituted pyrano[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines have also been prepared.

The considerable biological and medicinal activity of fused 4*H*-pyrans has stimulated much research in this field.[1–3] In continuation of our previous work[4–6] on the synthesis of fused pyrans using enaminonitriles, we report here the synthesis of a variety of new heterocyclic compounds. Thus condensation of various substituted α-cyanocinnamonitriles **1a**,**b** with 4-chloro-1-naphthol **2** in ethanolic piperidine afforded 1:1 adducts.[5,7,8] Structure **3** (Scheme 1) was established on the basis of the ^{1}H NMR spectra which showed 7-H at δ 5.1 (**3a**) and at δ 5.4 (**3b**).[5] The increased chemical shift for this signal, compared to the expected value (δ 4.0–5.0) for such protons, can be attributed to the deshielding effect of the diamagnetic current of the naphthyl, aryl and allylic π-electrons.[8–10] The UV spectrum of **3a** revealed a weak shoulder,[11] characteristic for a 4*H*-pyran at λ_{max} ($CHCl_3$) 275 (log ε 4.7).

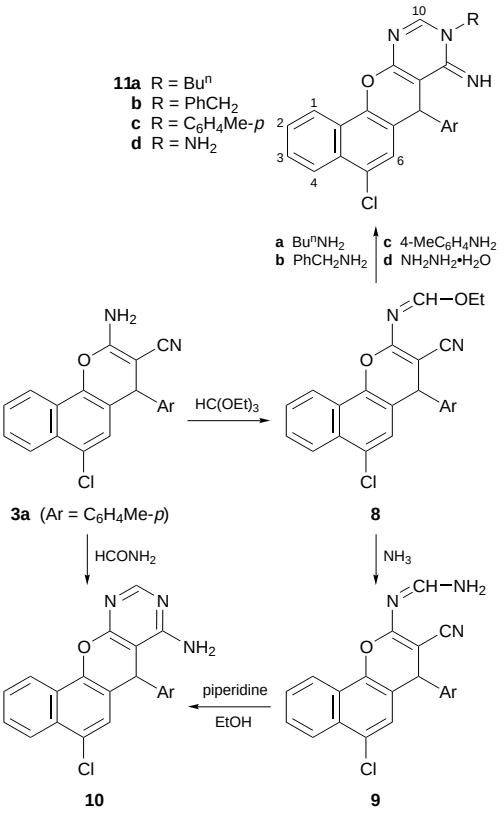


Scheme 1

Interaction of 2-amino-6-chloro-4-(*p*-tolyl)-4*H*-naphtho-[1,2-*b*]pyran-3-carbonitrile **3a** with acetic anhydride for 30 min afforded the *N*-acetyl **4** and *N*,*N*-diacetyl derivatives **5**, while heating of **3a** with acetic anhydride under reflux for 3 h afforded the naphthopyranopyrimidin-8-one derivative **6**. Structure **6** is supported by an independent synthesis of the same product from **3b** and acetonitrile in the presence of HCl gas[12] (Scheme 1). Structures **4–6** were established by spectral data and analogy with our previous work.[5] An attempted cyclization of **4** in ethanolic piperidine to give **6** failed.[5]

*To receive any correspondence.

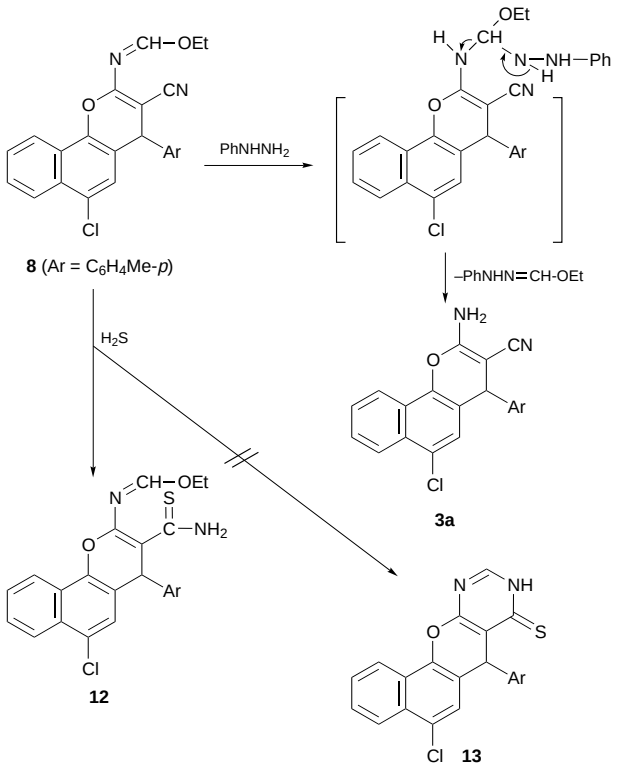
Treatment of **3a** with formic acid gave the naphtho-pyranopyrimidin-8-one derivative **7**. The structure of **7** was supported by an independent synthesis from **3b** and formamide (Scheme 1).



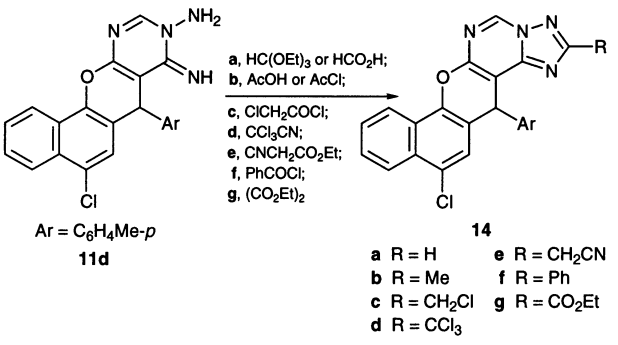
Scheme 3

Treatment of **3a** with triethyl orthoformate in acetic acid at reflux gave the corresponding ethoxymethylideneamino derivative **8** (Scheme 3), ammonolysis of which in methanol at room temperature afforded the open-chain product **9**. Treatment of **9** with ethanolic piperidine caused cyclization to yield the pyrimidine derivative **10**, the structure of which was supported by its independent synthesis from **3a** and formamide (Scheme 3). Reaction of **8** with various amines in ethanol at room temperature yielded the pyrimidine derivatives **11a–c**, while with hydrazine hydrate, the naphtho-[2′,1′:5,6]pyrano[2,3-*d*]pyrimidine derivative **11d** was obtained (Scheme 3).

When **8** was treated with phenylhydrazine in ethanol at room temperature, an addition product formed, from which elimination of ethyl formate phenylhydrazone gave the enaminonitrile **3a**,[14] while, with hydrogen sulfide, an addition product **12** formed, in which the hydrogen sulfide added into the cyano group only. Attempted cyclization of **12** in ethanolic piperidine to give **13** failed (Scheme 4).



Scheme 4



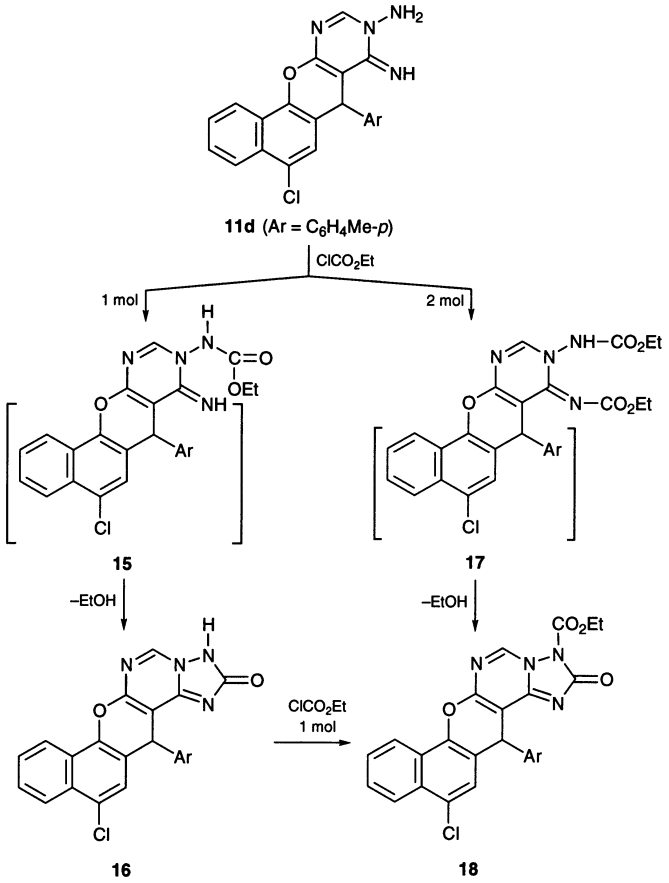
Scheme 5

Interaction of **11d** with triethyl orthoformate or formic acid afforded the naphtho[2′,1′:5,6]pyrano[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivative **14a**, while with acetic acid or acetyl chloride the respective 2-methyl derivative **14b** was obtained. Reaction of **11d** with chloroacetyl chloride and trichloroacetonitrile at reflux yielding the corresponding 2-chloromethyl **14c** and 2-trichloromethyl **14d** derivatives respectively, while with ethyl cyanoacetate and benzoyl chloride the 2-cyanomethyl **14e** and 2-phenyl **14f** derivatives were obtained (Scheme 5).

Treatment of **11d** with diethyl oxalate in ethanol at reflux yielded the 2-ethoxycarbonyl derivative **14g** (Scheme 5).

Treatment of **11d** with ethyl chloroformate in dry benzene afforded a 1:1 adduct **16**, while heating of **11d** with ethyl chloroformate under reflux for 3 h yielded a 1:2 adduct **18**. The formation of **16** is assumed to proceed *via* interaction of **11d** with ethyl chloroformate with elimination of HCl to yield **15**, which then cyclizes into **16** with elimination of ethanol. However, **18** is assumed to be obtained *via* formation of a bis(ethoxycarbonyl) derivative **17**, which cyclizes into **18** with elimination of ethanol (Scheme 6).

Techniques used: IR, UV, ^{1}H NMR, ^{13}C NMR, MS, microanalysis



Scheme 6

References: 14

Schemes: 6

Table 1: Characterization data for newly synthesized compounds

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